#### Online supplement to:

### Differences in coagulopathy indices in patients with severe versus nonsevere COVID-19: A Meta-analysis of 35 Studies and 6427 Patients

Alberto Polimeni<sup>1,2</sup>, MD, PhD, Isabella Leo, MD<sup>1</sup>, Carmen Spaccarotella<sup>1,2</sup>, MD, Annalisa Mongiardo<sup>1</sup>, MD, Sabato Sorrentino<sup>1,2</sup>, MD, PhD, Jolanda Sabatino<sup>1,2</sup>, MD, PhD, Salvatore De Rosa<sup>1,2</sup>, MD, PhD, Ciro Indolfi<sup>1,2,3</sup>, MD

#### **Affiliations:**

Division of Cardiology<sup>1</sup> and Center for Cardiovascular Research<sup>2</sup>, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy. Mediterranea Cardiocentro, Naples, Italy <sup>3</sup>.

#### **Supplemental Table 1 - MOOSE Checklist**

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition	Yes	4
Hypothesis statement	Yes	4
Description of Study Outcome(s)	Yes	7,8
Type of exposure or intervention used	Yes	5
Type of study design used	Yes	5
Study population	Yes	7
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians		- I
and investigators)	Yes	5
Search strategy, including time period		
included in the synthesis and keywords	Yes	4,5
Effort to include all available studies,		1.5
including contact with authors	Yes	5
Databases and registries searched	Yes	4
Search software used, name and	1.55	<u> </u>
version, including special features used	Yes	4
(eg, explosion)	100	
Use of hand searching (eg, reference		
lists of obtained articles)	Yes	5
List of citations located and those		7
excluded, including justification	Yes	7
Method for addressing articles		
published in languages other than	Yes	5
English		
Method of handling abstracts and	Yes	l 5
unpublished studies	res	
Description of any contact with authors	Yes	5
Reporting of Methods		
Description of relevance or		
appropriateness of studies assembled for	Yes	5
assessing the hypothesis to be tested		
Rationale for the selection and coding of		
data (eg, sound clinical principles or	Yes	5
convenience)		
Documentation of how data were		
classified and coded (eg, multiple raters,	Yes	5
blinding, and interrater reliability)		
Assessment of confounding (eg,		
comparability of cases and controls in	Yes	6
studies where appropriate		

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including		
blinding of quality assessors;	Yes	[-
stratification or regression on possible	165	5
predictors of study results		
Assessment of heterogeneity	Yes	6
Description of statistical methods (eg,		
complete description of fixed or random		
effects models, justification of whether		
the chosen models account for predictors	Yes	6
of study results, dose-response models,		
or cumulative meta-analysis) in sufficient		
detail to be replicated		
Provision of appropriate tables and	TV T	5.7.0
graphics	Yes	5,7,8
Reporting of Results		
Table giving descriptive information for	Yes	7
each study included	103	1
Results of sensitivity testing (eg,	Yes	
subgroup analysis)	res	8
Indication of statistical uncertainty of		
findings	Yes	7,8
Reporting of Discussion		
Quantitative assessment of bias (eg,	Yes	6
publication bias)	100	
Justification for exclusion (eg, exclusion		-
of non-English-language citations)	Yes	5
Assessment of quality of included studies	Yes	5
Reporting of Conclusions		
Consideration of alternative explanations	Yes	10
for observed results	103	
Generalization of the conclusions (ie,		
appropriate for the data presented and	Yes	9,10
within the domain of the literature review)		
Guidelines for future research	Yes	10
Disclosure of funding source	Yes	1

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.



### **PRISMA 2009 Checklist**

#### Supplemental Table 2 – Prisma Checklist

Section/topic	#	Checklist item	Reported on page #	
TITLE	<u> </u>			
Title	Title 1 Identify the report as a systematic review, meta-analysis, or both.			
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2	
INTRODUCTION	<del></del>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4	
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.		
Information sources	7 Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.		5	
Search	earch 8 Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.		5	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5,6	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5,6	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).		
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.	6	



### **PRISMA 2009 Checklist**

Section/topic	#	Checklist item	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7,8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION	<u>.</u>		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING	-		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

### **Supplemental Table 3 - QUALITY ASSESSMENT AHRQ**

	1	2	3	4	5	6	7	8	9	10	11
Cai Q.	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes	No	No	No
Chen G.	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes	No	No	No
Chen T.	Yes	Yes	Yes	Unclear	Unclear	Yes	No	No	No	Yes	No
Deng Q.	Yes	Yes	Yes	Unclear	Unclear	No	No	No	No	No	No
Gao Y.	Yes	Yes	Yes	Unclear	Unclear	No	No	Yes	No	No	No
Han H.	Yes	Yes	Yes	Unclear	Unclear	No	No	No	No	No	No
Huang C.	Yes	Yes	Yes	Unclear	Unclear	Yes	No	No	No	No	No
Huang H.	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	No	No	No
Li J.	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes	No	No	No
Li K.	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	No	No	No
Li Z.	Yes	Yes	Yes	Unclear	Unclear	Yes	No	No	No	No	No
Liu Jiacheng	Yes	Yes	Yes	Unclear	Unclear	No	No	Yes	No	No	No
Liu Jing	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes	No	No	No
Lu H.	Yes	Yes	Yes	Unclear	Unclear	No	No	No	No	No	No
Lu Z.	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	No
Luo X.	Yes	Yes	Yes	Unclear	Unclear	No	Yes	No	No	No	No
Ма К.	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	No
Qian G.	Yes	Yes	Yes	Unclear	Unclear	No	No	No	Yes	No	No
Tang N.	Yes	Yes	Yes	Yes	Unclear	No	No	Yes	No	No	No
Wan S.	Yes	Yes	Yes	Unclear	Unclear	No	No	Yes	No	No	No
Wang D.	Yes	Yes	Yes	Yes	Unclear	No	No	No	No	No	No
Wang K.	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes	No	Yes	No
Wang L.	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	No	No	No
Wu C.	Yes	Yes	Yes	Unclear	Unclear	No	No	No	Yes	Yes	No
Wu J.	Yes	Yes	Yes	Unclear	Unclear	No	No	Yes	No	No	No
Xu Y.	Yes	Yes	Yes	Yes	Unclear	No	Yes	No	No	No	No
Zeng J.	Yes	Yes	Yes	Unclear	Unclear	No	No	No	No	No	No
Zhang F.	Yes	Yes	Yes	Yes	Unclear	No	Yes	No	No	No	No
Zhang G.	Yes	Yes	Yes	Unclear	Unclear	No	No	No	Yes	No	No
Zhang J.	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes	No	No	No
Zheng C.	Yes	Yes	Yes	Unclear	Unclear	No	No	No	No	No	No
Zheng X.	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	No	Yes	No
Zhou F.	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	No	No	No
Zhou Ying	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	No
Zhou Yulong	Yes	Yes	Yes	Unclear	Unclear	No	No	Yes	No	No	No

1) Define the source of information; 2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications;3) Indicate time period used for identifying patients;4) Indicate whether or not subjects were consecutive if not population-based;5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants;6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements);7) Explain any patient exclusions from analysis;8) Describe how confounding was assessed and/or controlled.;9) If applicable, explain how missing data were handled in the analysis;10) Summarize patient response rates and completeness of data collection;11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained

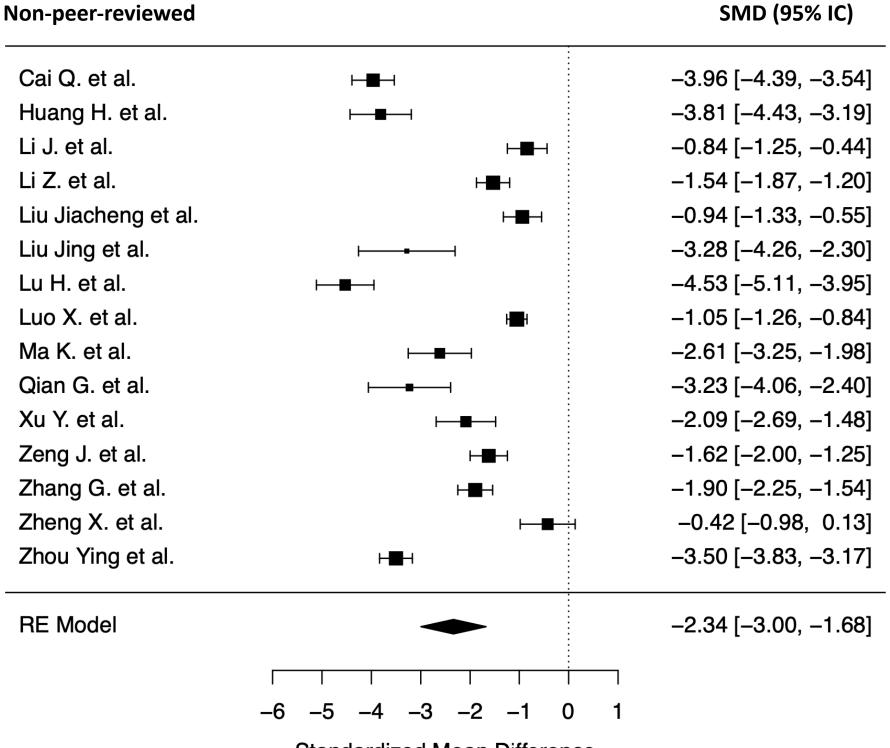
### A D-dimer

#### **Non-Severe vs Severe**

Peer-reviewed		SMD (95% IC)
Chen G. et al.	<b>├─</b> ■─┤	-1.36 [-2.31, -0.41]
Deng Q. et al.	H■■H	-1.18 [-1.59, -0.77]
Gao Y. et al.	<del></del>	-2.21 [-2.99, -1.43]
Han H. et al.	H <b>≣</b> H	-0.73 [-1.18, -0.29]
Huang C. et al.	<b>⊢</b> ■→	-1.87 [-2.64, -1.10]
Wan S. et al	H <b>≣</b> H	-2.95 [-3.46, -2.44]
Wang D. et al.	H <b>≣</b> H	-1.71 [-2.14, -1.28]
Wu C. et al.		-1.22 [-1.53, -0.92]
Wu J. et al.	<del>⊢■</del> -1	-7.30 [-7.96, -6.64]
Zhang J. et al.	H <b>≡</b> H	-0.57 [-0.91, -0.22]
Zheng C. et al.	<b>⊢=</b> -1	-1.70 [-2.32, -1.07]
Zhou Yulong et al.		0.09 [-0.96, 1.13]
RE Model		-1.90 [-2.95, -0.84]
	-8 -6 -4 -2 0 2	
	Standardized Mean Difference	

### **B** D-dimer

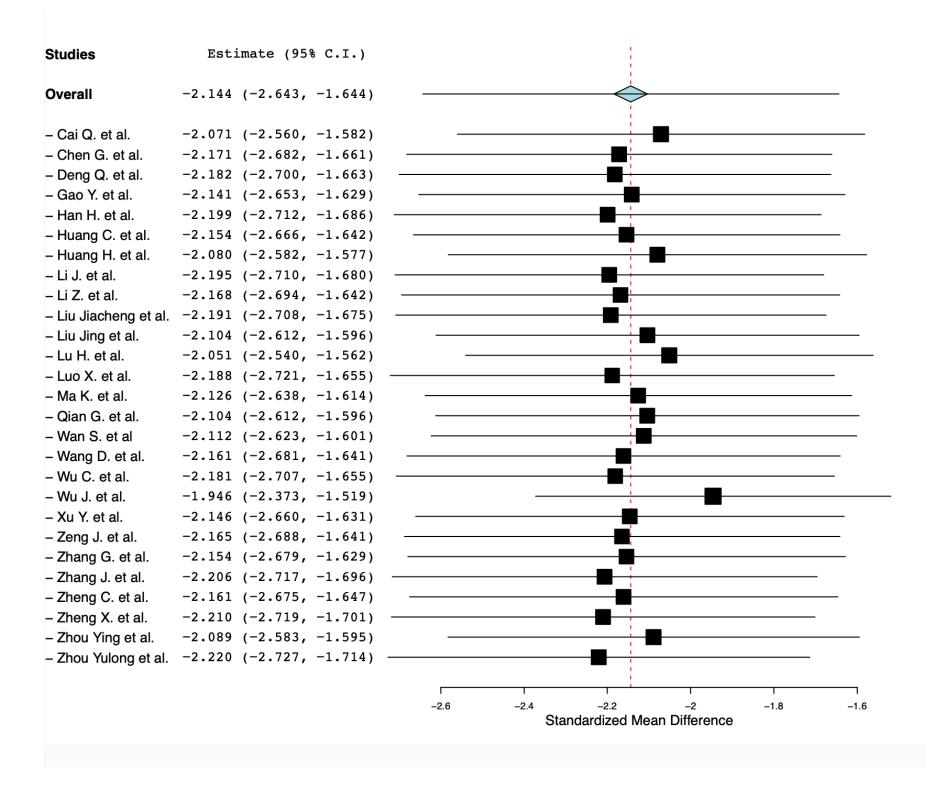
### **Non-Severe vs Severe**



Standardized Mean Difference

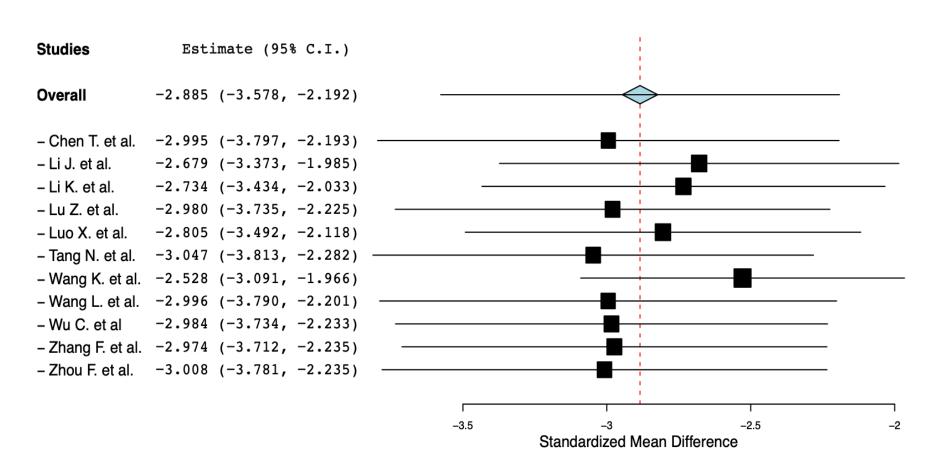
## **A** Sensitivity Analysis for D-dimer outcome

#### Non-Severe vs Severe

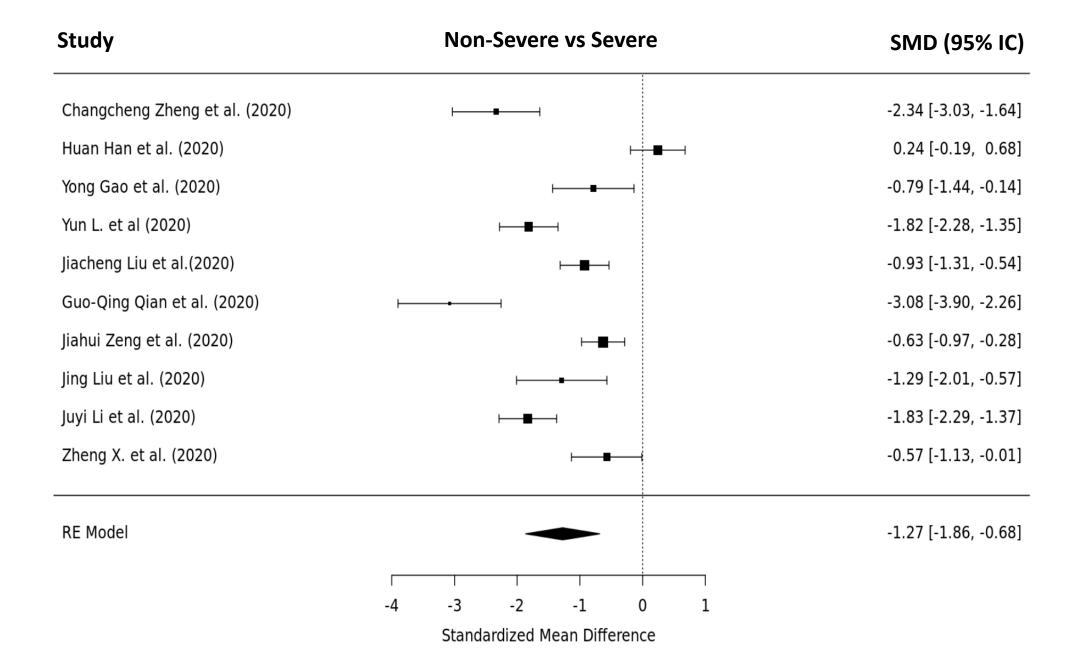


## **B Sensitivity Analysis for D-dimer outcome**

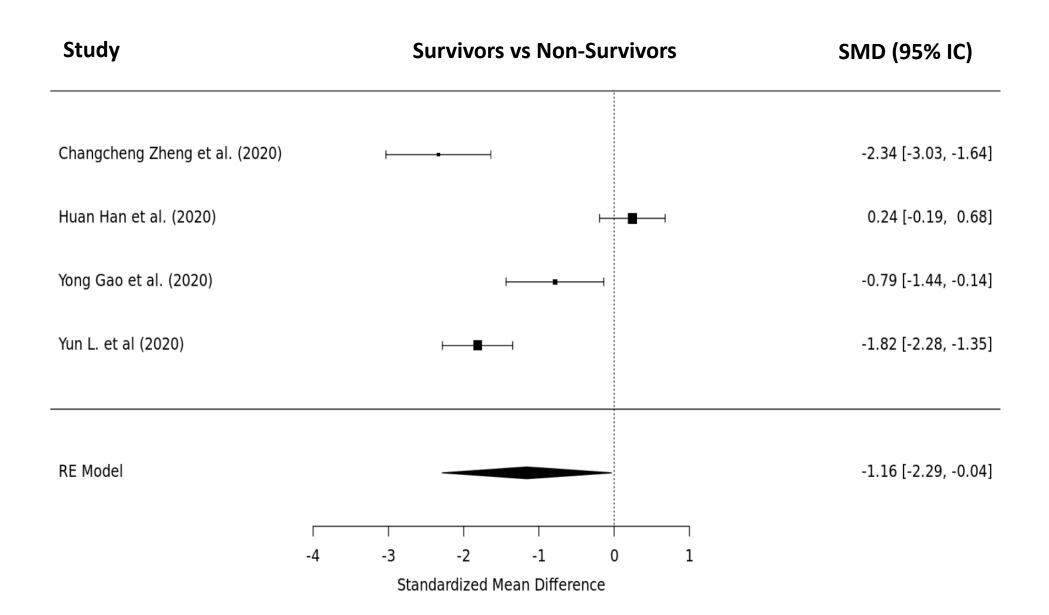
#### **Survivors vs Non-Survivors**



## A Fibrinogen



## **B** Fibrinogen



# **Fibrin Degradation Product**

Study	Non-Severe vs Severe	SMD (95% IC)
Channel and 7hannah at (2020)		1 25 ( 1 05 - 0 66)
Changcheng Zheng et al (2020)	<b>├──</b>	-1.25 [-1.85, -0.66]
Huan Han et al (2020)	<b>⊢-■</b> →	-0.73 [-1.18, -0.29]
Lu H. et al (2020)	<b>├──</b>	-5.17 [-5.79, -4.55]
RE Model		-2.38 [-5.13, 0.36]
	-6 -5 -4 -3 -2 -1 0	
	Standardized Mean Difference	

# **International Normalized Ratio (INR)**

Study		Non-Severe vs Severe				SMD (95% IC)	
Jiacheng Liu et al (2020)		<b>⊢</b>	$\dashv$			-1.76 [-2.19, -1.33]	
Huan Han et al (2020)			<b>⊢—</b>			-0.56 [-1.00, -0.12]	
Jing Liu et al (2020)			<b>⊢</b>		<b>⊣</b>	0.00 [-0.66, 0.66]	
Juyi Li et al (2020)			<b>⊢</b>			-0.55 [-0.95, -0.16]	
RE Model						-0.74 [-1.46, -0.02]	
	-3	-2	-1	0	1		
		Standard	dized Mean Di	fference			

